

## **REMARKS**

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

### **I. AMENDMENT TO THE SPECIFICATION**

In the specification, paragraphs have been amended on pages 20-22. The amendments correct typographic and nomenclature errors in certain names assigned to disclosed structures. Support for the changes can be found in the corresponding disclosed structures.

### **II. STATUS OF THE CLAIMS**

Claims 1-54, and 61, 65, and 73-77 are requested to be canceled.

Claims 62-64, 66-72, 78-81 are currently amended.

Claims 82-97 are being added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 62-64, 66-72, and 78-97 are now pending in this application.

### **III. ELECTION/RESTRICTION REQUIREMENT**

In the previous response dated July 15, 2005, Applicants elected modified group II with the species of Example 080 for examination.

The Office stated that the example 080 is not embraced by independent claim 1 (pages 2-3 of the Office Action). In light of this instant amendment to the claims, the elected species is believed embraced by independent claims 67, 83, and dependent claims 85, 86 and 87.

Specifically, Applicants have amended the claims to replace “a nitrogen atom” with “**a pendant basic nitrogen functionality**” which was recited in the original claims and supported by the specification. Moreover this comports with a reasonable construction in light of the specification, especially the examples. As explained in more detail below, a person of ordinary skill in the art would recognize that “a pendent basic nitrogen

functionality” includes “4-methyl-piperazin-1-ylmethyl” group. Therefore the elected species is embraced by independent claims 67 and 83.

#### IV. REJECTIONS UNDER 35 U.S.C. § 112

##### A. Claims 62-72

In the Office Action, the Office has made several rejections under § 112 for alleged indefiniteness (pages 12-14 of the Office Action). Applicants have amended these claims to render moot the indefiniteness rejections. The Office has not made any rejections of claims 62-72 under § 102 or § 103.

Specifically, in claims 62-64, and 66-67, the language “a nitrogen atom” is amended to be “**a pendant basic nitrogen functionality.**” The language “a pendant basic nitrogen functionality” was in the original claims and in the specification, for example, page 4 lines 3, 6 and 10, and page 5, lines 6 and 21.

Claims 62 and 66 are redrafted in independent form; therefore, the ground of lacking antecedent basis from claim 1 is moot.

Claim 63-64 are redrafted in independent form; therefore, the rejections on the ground of lacking antecedent basis from claim 1, and the rejection on the ground that R is defined differently in claim 1 (i.e.  $-\text{SO}_2\text{R}$ ”), are moot.

Claims 63-64 are amended to make clear that  $-\text{COR}'$  and  $-\text{CONR}'\text{R}$ ” are defining R, not R”.

Claim 65 is canceled and a new independent claim 94 is added which corresponds to the canceled claim 65.

Claim 67 is amended to add more functional groups (namely,  $\text{NO}_2$  and CN) to the Markush group for  $\text{R}^6$ . Support can be found in specification example compounds 117 and 081, respectively. Claim 67 is also amended to become an independent claim, therefore, the rejection on the ground of lacking antecedent basis from claim 1 is moot.

Claim 68 is amended to delete the species of examples 009, 011, 013, 014, 016, 017, 018, 021, therefore mooting the ground of lacking antecedent basis in claim 67. Because claim 67 is amended to become an independent claim, the ground of claim 69 lacking antecedent basis in claims 1 and 67 is moot.

Claim 69 is amended to clarify that X is selected from (a)-(f).

Claims 70-72 are amended to change their dependency to claim 69 from claim 67, therefore the ground of lacking antecedent basis is moot.

Additionally, claim 68 is amended to insert the example numbers designated to the compounds.

**B. Claims 78-81**

The Office asserts that claims 78-81 lack antecedent basis from claim 1 (page 14 of the Office Action).

Applicants have amended claim 78-81 to change their dependency to claim 67 from claim 1, therefore the ground of lack of antecedent basis in claim 1 is moot.

Additionally, claims 78-81 are amended to insert the example numbers designated to the compounds.

**C. New claims 82-97**

Applicants have canceled claims 1, 61, 65, 73-77 and added new claims 82-97. No new matter is introduced.

New claim 82 claims a composition comprising the compound shown in example 066.

New claim 83 corresponds to the canceled claim 1, wherein the “a nitrogen atom” language is changed to “a pendant basic nitrogen functionality.” In rewriting the claim, the Applicants have incorporated the changes suggested by the Office at page 8, line 15, to page 10, line 3, of the Office Action.

Additionally, new claims 85, 88, and 91 are directed to the subgenuses of claim 83. Claims 86, 89, and 92 are directed to species which fall into claims 85, 88 and 91. Additionally, the example number designated to the species is inserted at the end of each compound name.

New claims 89, 90, and 93 are directed to pharmaceutical compositions.

New claim 94 is added, which corresponds to the canceled claim 65. New claim 95 recites species.

New claim 96 is dependent from claim 63 and recites species.

New independent claim 97 covers other species exemplified in the specification.

**D. The term “a pendant basic nitrogen functionality” is not indefinite**

Applicants have amended a number of claims to recite “a pendant basic nitrogen functionality” instead of “a nitrogen atom” in response to the Office’s rejections on the ground that “a nitrogen atom” is indefinite. The recitation “a pendant basic nitrogen functionality” is in the specification and was in the original claims, therefore no new matter is introduced.

The recitation “a pendant basic nitrogen functionality” is not indefinite because its plain meaning can be ascertained by those ordinary skilled in the art in light of common usage in the field and ample exemplary compounds in the specification.

As explained in *Exxon Research & Eng’g Co. v. United States*, if the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, the claim should be held sufficiently clear to avoid invalidity on indefiniteness grounds. 265 F.3d 1371, 1375 (Fed. Cir. 2001). Thus, the inventive contribution of patentees should be protected, even when the drafting of their patents has been less than ideal. *Id.* at 1375.

The recitation “a pendant basic nitrogen functionality” is not insolubly ambiguous, and therefore should not be held indefinite.

Applicants submit herewith a declaration by Marco Ciufolini (Declaration (II) with detailed statements explaining that “nitrogen functionality” can be clearly understood by a person skilled in the art. See Declaration (II) paragraphs 18-26.

Applicants believe that the amended claims as such have overcome the rejections under 35 U.S.C. § 112 on each of the grounds. Therefore Applicants respectfully request reconsideration and withdrawal of the rejections.

**V. REJECTION OF CLAIMS 1, 54, 61 AND 73-76 UNDER 35 U.S.C. § 103(a)**

The Office rejected claims 1, 54, 61 and 73-76 as allegedly obvious over Dexter (U.S. Patent No. 3,467,666), Spivak (U.S. Patent No. 6,291,514), Illig (U.S. Patent No. 6,291,514) and Dhanoa (U.S. Patent Publication No. 2001/0044545).

The Office stated that the declaration under 37 C.F.R. § 1.132 filed on February 27, 2007 (Declaration (I)) is insufficient to overcome the rejections of claims 1, 54, 61 and 73-76 under 35 U.S.C. § 103. The Office’s grounds are (1) that the showing is not commensurate

with the scope of the instant claims (page 4 of the Office Action), (2) that the compounds listed in the declaration are not embraced by then amended claim 1 (page 5 of the Office Action); and (3) that the Illig compound being difficult to make may implicate lack of enablement of the instant claim (pages 5-6 of the Office Action).

After the instant amendment made to the claims, the listed compounds in Declaration (I) are embraced by the new claims. This addresses the Office's point (2) above.

Applicants submit herewith a second declaration (Declaration (II)) which presents data on a large number of compounds claimed by the present application and the Illig compound cited by the Office. Declaration (II) addresses the Office's points (1) and (3).

The instant amendment to the claims cancels claims 1, 54, 61, 65, and 73-76, and adds new claims 82-97. New claim 83, having modified R1's definition, corresponds to canceled claim 1. Applicants modify R1's definition solely for advancing the prosecution of this application without prejudice and disclaimer.

The new claims are not obvious over the cited references.

**A. The claimed compounds have unexpected properties**

Even if a *prima facie* case of obviousness were properly made out, which Applicants do not concede for the reasons presented below, the unexpected properties of the claimed compounds would rebut such a *prima facie* case.

As explained in MPEP § 716.02(d) paragraph I:

“[t]he nonobviousness of a broader claimed range can be supported by evidence base on unexpected results from testing a narrower range if one of ordinary skilled in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof. *In re Kollman*, 595 F.2d 48, 201 USPQ 193 (CCPA 1979).”

Applicants submit herewith a declaration by Marco A. Ciufolini (Declaration II), one of the named inventors, demonstrating unexpected properties of the claimed compounds commensurate with the scope of the claims. The compounds tested and presented in the Declaration (II) represent compounds with a wide range of variables. In light of the scope of the Markush group recited for each of the variables, the tested compounds sufficiently allow the ordinary skilled in the art to determine the range in the exemplified data which allow them to extend the probative value to the compounds claimed but untested.

The Illig compound shows no inhibitory activity on any type of c-kit tested and has no selectivity toward any type of c-kit in the experiment. *See* Ciufolini Declaration (II) Table 1 and paragraph 12. In contrast, the claimed compounds demonstrate a high potency and specificity in c-Kit inhibition. *See* Declaration (II) Table 2 and paragraph 15.

Similarly, the Dexter compound, the Spivak compound, and the Dohana compound lack the potency and specificity of the claimed compounds. *See* Ciufolini Declaration (I) of record, Table 1 and paragraphs 11 and 14.

This selectivity of the claimed compounds has important practical applications. *See* Ciufolini Declaration (II) at paragraph 16. For example, the high degree of selectivity allows the claimed compounds to be effective against diseases characterized by expression of particular forms of c-kit. *Id.* Expression of wild-type c-kit is associated with conditions such as inflammatory diseases and autoimmune diseases. Thus, inhibitors of wild-type c-kit can be used to treat these conditions. Expression of mutated c-kit is associated with conditions such as the aggressive forms of mastocytosis. Thus, inhibitors of mutated forms of c-kit can be used to treat these conditions. *See* Ciufolini Declaration (II) at paragraph 16. In other words, the selectivity allows the compounds to be clinically applied to treat a variety of conditions implicating c-kit.

Nothing in the prior art suggests that the claimed compounds would possess the selective inhibition of c-Kit described in the Ciufolini declarations. Accordingly, the claimed compounds exhibit unexpected results over the prior art. The unexpected results sufficiently rebut any *prima facie* case of obviousness.

**B. Spivak and Dexter cannot be relied on in evaluating obviousness of the present invention because they are not analogous art.**

As explained by the MPEP:

The examiner must determine what is “analogous prior art” for the purpose of analyzing the obviousness of the subject matter at issue. “In order to rely on a reference as a basis for rejection of an applicant’s invention, the reference must either be in the field of applicant’s endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned.” *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

MPEP § 2141.01(a) I. The MPEP further explains what is analogy in chemical arts in § 2143.01(a) III.

Spivak describes compounds useful in stabilizing fatty materials. (Spivak, col. 3 lines 18-26). Dexter describes compounds useful as chemical intermediates, and for stabilizing unstable chemical materials, and as muscle relaxant (Dexter, col 3, lines 33-40). However, the present invention is concerned with compounds as c-Kit inhibitor.

Spivak and Dexter are unrelated to c-kit inhibitor technology and thus are not analogous art reference. The use as muscle relaxant described in Dexter is at best a throw-away, non-substantial utility. Thus, Spivak and Dexter should not be considered in the determination of obviousness of the present invention.

**C. There is no motivation to arrive to the instant invention.**

There is no teaching or suggestion in the art to modify the references to arrive at the claimed invention. The Office contends that the motivation “derives from the expectation that structurally similar compounds would possess similar activities.”

Applicants respectfully traverse. Drug design is unpredictable. In evaluating obviousness, predictability of the art must be considered. If the technology is unpredictable, it is less likely that structurally similar species are obvious because it would not be reasonable to infer that they would share similar properties. *In re May*, 574 F.2d 1082, 1094, 197 USPQ 601, 611 (CCPA 1978), MPEP § 2144.08 II.A.4(e).

Homology or structural similarity must be considered with all other relevant facts in determining obviousness. *In re Mills*, 281 F.2d 218, 126 USPQ 513 (CCPA 1960); *In re Wiechert*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967). Homology should not be automatically equated with prima facie obviousness because the claimed invention and the prior art must each be viewed “as a whole.” *In re Langer*, 465 F.2d 896, 175 USPQ 168 (CCPA 1972); MPEP § 2144.09. When evaluating the scope of a claim, the claimed invention should not be dissected into discrete elements to be analyzed in isolation, but must be considered as a whole. *See, e.g. W.L.Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983); *Jones v. Hardy*, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1983); MPEP § 2144.08.I.

The references do not disclose compounds having a similar activity. Spivak describes compounds useful in stabilizing fatty material. (Spivak, col. 3 lines 18-26). Dexter describes compounds useful in stabilizing unstable chemical materials and as muscle relaxant (Dexter, col 3, lines 33-40). Illig discloses compounds as inhibitors of proteases, especially trypsin-like serine protease (Illig, abstract). Dohanoa describes compounds as PAI-1 inhibitors (Dhanoa, abstract). The instant claimed compounds are, however, inhibitors of c-Kit.

The present invention is targeting biological activity and medical indication very different from what Illig or Dhanoa is targeting, or what Spivak or Dexter is targeting. Considered with these relevant facts, any structural similarity alleged by the Office does not establish a *prima facie* case of obviousness on the homology rationale.

For all the reasons presented above, Applicants respectfully submit that no *prima facie* case of obviousness is made out by the art of record.

## **VI. THE DOUBLE PATENTING REJECTIONS**

The Office has provisionally rejected claims 1, 54, 61-76, and 78-81 over claims 1-22 of the co-pending application 10/523,018 and over claims 31-32 of co-pending application 10/567,557 (page 16 of the Office Action).

While Applicant does not acquiescence to the Office's reasoning or conclusion, the applicants respectfully request the Office to hold this provisional rejection in abeyance until such time as the claims at issue are deemed otherwise allowable.

## **CONCLUSION**

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

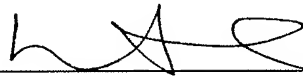
The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to



charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: September 10, 2007

By  \_\_\_\_\_

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